MANIFOLD BASED MORPHOMETRY APPLIED TO SCHIZOPHRENIA

Ragini Verma[1], *Parmeshwar Khurd*[1], *James Loughead*[2], *Raquel Gur*[2], *Ruben Gur*[2] *and Christos Davatzikos*[1]

[1]{Section of Biomedical Image Analysis, Department of Radiology}, [2]{Brain Behavior Laboratory, Department of Neuropsychiatry} University of Pennsylvania

Ragini.Verma@uphs.upenn.edu

ABSTRACT

The growing clinical importance of Diffusion tensor imaging (DTI) in disease investigation has prompted large population studies that require computational neuroanatomic techniques for tensor processing, as conventional analysis of scalar maps of DTI does not identify the full impact of pathology. In this paper we propose a comprehensive framework called Manifold Based Morphometry (MBM) for the computational and statistical analysis of DTI datasets, consisting of spatial normalization to a template, followed by voxel-based analysis based on embedding the tensors to a linear submanifold using kernel-based manifold learning and applying statistics in this embedded space. Regions of significant difference are identified and compared with those found with conventional voxel-based analysis of scalar maps of anisotropy and diffusivity. MBM has then been applied to the group-based statistical analysis of dataset of schizophrenia patients and controls. The comparison yields that MBM consisting of the full tensor DTI analysis reveals regions of difference that encompass regions identified by the analysis of scalar maps thereby reinforcing the comprehensive nature of the designed framework.

Index terms - Diffusion Tensor Imaging, manifolds, statistics, voxel-based analysis, population study, schizophrenia

1. INTRODUCTION

DTI [1] has gained wide acceptance as an MR modality that provides a non-invasive index of WM micro-structural integrity [2], and anatomical connectivity [3], by quantifying the magnitude and directionality of microscopic water diffusion in the WM, and is being increasingly used in the investigation of WM diseases. However, DTI may have an even more crucial role to play in the study of neuropsychiatric disorders such as schizophrenia [4], where conventional radiological evaluations fail to detect substantial WM differences. The growing clinical importance of DTI in disease investigation has prompted large population longitudinal and cross-sectional studies of WM changes in the brain, which can lead to early diagnosis of disease or to a more effective monitoring of treatment. This has generated a need for sophisticated computational neuroanatomic techniques for processing and statistically analyzing DTI data, in order to identify and quantify complex patterns of structural changes associated with inter-individual variability and those induced by pathology. While such techniques have been successfully developed for analysis of conventional structural MR images [5], their development for DTI data is challenging due to its high dimensionality and complex and non-linear underlying structure. These issues also make linear methods of statistical analysis developed for structural MR images [5], inapplicable to DTI data.

In the absence of established computational neuroanatomy tools for analyzing DTI data, current studies address DTI analysis by analyzing the scalar maps of anisotropy and diffusivity computed from the spatially normalized DTI data of the population. These scalar maps have been analyzed using ROI based methods that require appropriate a priori knowledge of regions of deficit, or by voxel-based morphometric methods applied to scalar maps [5]. While this analysis may be repeated for all scalar maps, correlating results across the various scalar maps, each of which may provide a unique region of significant difference, fails to reveal the full impact of pathology on tensor data. Recognizing the shortcomings of the existing DTI analysis approaches, in this paper we try to address and alleviate these issues by developing a paradigm for a full voxel-based analysis of the tensor data called Manifold Based Morphometry. Following spatial normalization of the DTI data, the crux of our framework lies in our novel method for voxel-based statistical analysis of tensors that learns the underlying statistical distribution of the tensor data and embeds it into a kernelized linear space on which linear statistics can be applied to identify regions of difference. These regions are then tested for multiple comparisons with a used defined threshold. The regions that survive are regions with most significant difference. In the subsequent sections, we give details of the MBM framework (section 2), describe application of these methods to schizophrenia dataset and discuss results (section 3), followed by the conclusions and summary (section 4).

2. MBM: COMPUTATIONAL NEUROANATOMY OF DTI

We have developed a comprehensive framework for the group-based analysis of DTI data called Manifold Based Morphometry. Suppose the population consists of N subjects. These could be grouped on the basis of pathology: patients and controls, gender etc. It consists of two stages: Stage 1: spatial normalization of the DTI data of the groups to a template using deformable registration, Stage 2: voxel-based application of tensor manifold analysis, that facilitates tensor statistics and produces regions of significant difference. Each of these stages is described in greater detail below.

2.1. Stage 1: Spatial Normalization

One of the study subjects is chosen as a template, to which all the DTI datasets are spatially normalized. DTI spatial normalization is particularly challenging as in addition to estimating a local deformation, either rigid or non-rigid, between the subject and the template, tensors must also be reoriented consistent with the underlying anatomical structure. Existing methods for registration of DT images are based on registering some scalar map computed from the tensors (e.g. fractional anisotropy (FA) and trace) [6, 7] followed by tensor reorientation, or by incorporating registration and reorientation into a multi-channel approach [8]. For our experiments, we have adopted a well validated method of DTI registration based on the registration of FA images [6]. Prior to applying the voxel based analysis, we smoothed the DTIs using Gaussian smoothing (with sigma=4 mm) in the Log-Euclidean domain [9]. The scalar maps of FA and trace have been equivalently smoothed so that the analysis is comparable.

2.2 Stage 2: Manifold-based analysis

Developing methods for an integrated analysis of DTI involving statistics of the data is challenging because tensors are restricted to lie on a non-linear sub-manifold of the space R^6 that needs to be determined along with defining a geodesic distance along the manifold that would replace Euclidean distance in the linear space, and which could then be used to define tensor combinations. We have developed several methods that estimate the underlying manifold structure using manifold learning [10] or by estimating the distribution through kernel based methods [11]. While either of the methods are applicable to large studies – however in the case of kernel based methods, we are sure that the underlying data at each voxel has been Gaussianized.

Kernel-based Manifold Learning We use kernel-based techniques to implicitly learn the underlying manifold structure of a set of tensors and their statistical distribution. In our case this set represents the tensor measurements at a given voxel from these N individuals that have been spatially normalized to the template. Kernel principal component analysis (kPCA) can effectively learn the probability density of the tensors under consideration. In addition kernel Fisher discriminant analysis (kFDA) can find features that can optimally discriminate between groups. Mathematical details of the process of learning the distribution using kernels can be found in the paper [11], along with studies to determine sensitivity of kernel-based learning to noise in the tensor data and its ability to determine the statistical distribution of the data.

Statistical Analysis We apply kPCA on the voxel-based samples to obtain highly informative projections. We then apply the kFDA technique which finds scalar projections onto a single RKHS direction that can optimally discriminate between groups. The projections found by the application of kPCA and kFDA are linear and linear multivariate statistics can be applied to this data. Having obtained our kernel-based features, we then apply the two-sided t-test in the case of the kFDA, in order to obtain a voxel-wise p-value map. It may be noted that the Hotelling test cannot be applied to non-linear high dimensional data, and hence the data was embedded to a linear kernelized space prior to the application of the statistical test. We then correct the p-value maps for multiple comparisons in a non-parametric manner via permutation tests and without any distributional assumptions [12, 13] by controlling the false discovery rate (FDR) [13] using a suitable p-value threshold. We then perform connected component analysis on this binary image and drop the components or clusters that contained very few voxels and are spurious clusters occuring due to noise.

In summary, the framework of Manifold Based Morphometry for the DTI analysis of large population studies, consists of the following steps: 1) spatial normalization of the DTI to a template, followed by 2) application of manifold-based analysis to tensors voxel-wise across the whole population, and 3) applying T-test to these kernelized datasets to identify regions of significant difference, that are then tested using FDR based on a user-defined threshold. In the next section, we apply our framework to study a dataset of schizophrenia patients and matched healthy controls.

3. RESULTS AND DISCUSSION

We have applied MBM to the DTI data of schizophrenia patients. We also perform conventional DTI analysis on these images.

3.1 Schizophrenia Dataset

The dataset consists of 34 patients (21 male and 13 female) and 36 healthy controls (17 male and 19 female). The controls are matched to the patients by age, sex and ethnicity.

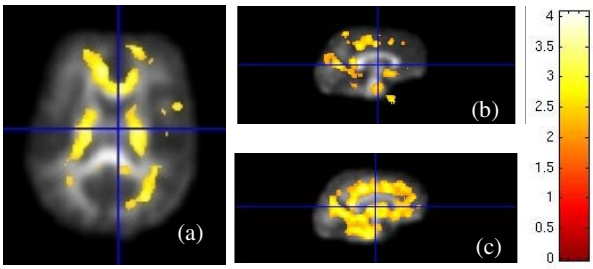

Fig. 1: SPM analysis of spatially normalized FA maps reveals differences between patients and controls in internal capsule in males (a) and in the cingulum in females (b). (c) shows differences between the whole patient and control population without considering gender.

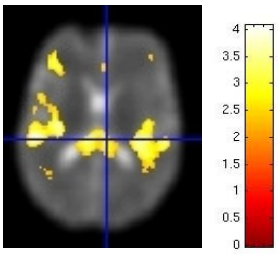

Fig. 2: SPM analysis of spatially normalized ADC maps reveals differences between patients and controls in gray matter regions

3.2 Group-based analysis of FA- and ADC scalar maps

The FA and ADC maps were created for each subject and warped to one of the healthy controls, chosen to be the template for this study. We then performed SPM-based [14] analysis on these spatially normalized FA and ADC maps separately and studied the interaction between patients and healthy controls, genderwise. Several regions showed group as well as sex differences at $p = 0.01$ and SPM smoothing of 10, indicative of trends of change. In Fig. 1(a), we see regions of difference between FA maps of male patients and controls, especially in the internal capsule and the genu of the corpus callosum. Fig. 1(b) shows regional changes in female patients and controls especially in the corona radiata. In Fig. 1(c) we see trends of collective group difference in the WM regions. Fig. 2 shows the predominantly GM regions of difference in the ADC maps. This analysis shows that different regions are identified by different scalar maps and with several more scalar maps possible, it is difficult to get a comprehensive picture of the effect of pathology from the independent analysis of these scalar maps. Also none of these regions were significantly different and permutation testing was not used.

3.3 Kernel-based tensor analysis

We applied MBM (as described in section 2.2) to the spatially normalized DTI datasets. Subsequently on applying the T-test followed by FDR we obtain a p-map of the levels of change. None of the regions showed up to be highly significant. As the sample size is small for high dimensional statistics estimation, we should consider these regions as trends of change. Fig. 3 shows regions with $p < 0.1$ (in the p maps generated as a result of applying voxel-based tensor statistics) indicating trends of change in several WM and GM regions. The analysis shows that female patients versus controls demonstrate differences in the corpus callossum, corona radiata, posterior limb of the internal capsule, cortico-spinal tract, insula, Heschl's gyrus and large regions of the temporal lobe. In males, prominent regions of change are the caudate, putamen, corpus callossum. The GM regions show a lateralization of effect as can be in the figure. Fig. 3(a – c) shows changes in females, 3(d) in males and 3(e) when all the subjects are taken together without gender being accounted for. Along with the changes in WM, prominent GM regions are also identified. Differences become more pronounced in the analysis of females, although the combined map shows changes in the temporal and occipital lobes.

4. DISCUSSION AND CONCLUSIONS

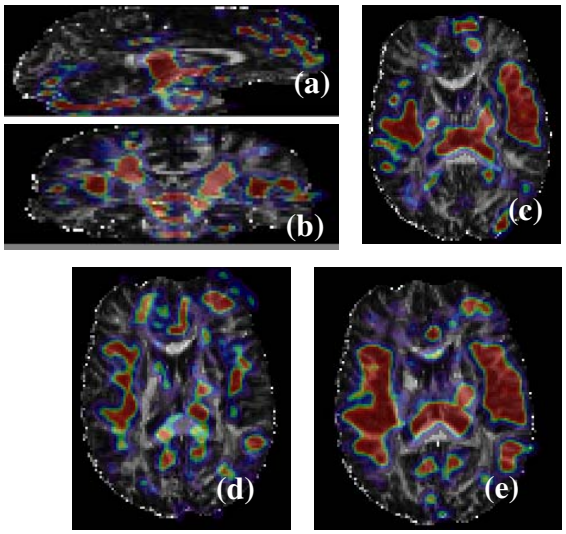

Fig. 3: Kernel- based analysis applied to the full brain and regions with p-value < 0.01 overlaid on the FA map. Regions of difference: (a-c) female patients and controls, (d) male patients and controls (e) all patients and controls. Red indicates higher significance than blue regions with more changes seen in females.

Structural MRI studies in schizophrenia [15] have demonstrated regional brain abnormalities, especially in the gray matter. DTI-based research in schizophrenia [16] has revolved around studying WM changes and possible abnormalities in inter-hemispheric connectivity through the corpus callossum and intra-hemispheric connectivity between frontal, temporal and occipital lobes via association fibers. Study is mainly based on FA and ADC values of specific regions under study or voxel based analysis as

described above in section 3.2. The application of MBM method for tensor analysis produces a comprehensive map of change, both in the white matter and the gray matter, covering most of the regions identified by the analysis of FA and ADC maps, along with additional regions, thereby demonstrating its significance for DTI analysis.

Some of the important regions identified by MBM are regions in the corpus callosum which is responsible for the left-right connectivity in the brain, parts of the cortico-spinal tract, disruption of which are responsible for motor function deficit, internal capsule, parts of the insula and limbic region which are responsible for emotion processing, as well as the temporal lobe, which is involved in high-level visual processing of complex stimuli such as faces and scenes, as well as spatial memory, have shown significant deficits in our analysis. As deficits in perception, emotion, behavior and memory are deficits related to schizophrenia and since the regions identified compares with the regions hypothesized to change in schizophrenia, it establishes the significance of the full tensor analysis, which presents a unified comprehensive picture.

MBM on DTI has produced comprehensive results of group differences, identifying differences in regions and tracts, some of which have also been identified by other disjoint conventional methods (FA and fiber tracking) independently. However as can be seen we need both FA and ADC analyses, as neither of them showed all the differences simultaneously. The full tensor analysis via MBM also shows additional regions and tracts of change. Thus it is beneficial to do this, as compared to analyzing all possible scalar maps from DTI data and performing individual voxel-based analysis on these. We propose to correlate these regions of change with neuropsychiatric scores or other clinical measures of deficit, to correlate the effect of pathology. This will indicate the clinical applicability and utility of this DTI processing paradigm. Also, we are expanding the size of the dataset, to identify whether the regions that show trends of change but are not significant, demonstrate significant difference in a larger dataset. We are also applying this method to other diseases in which changes are not too subtle.

In summary, we expect that a comprehensive examination of any disease using the DTI processing pipeline that we propose called MBM, will elucidate subtle regional changes and subtle disruptions of connectivity. We expect that in long-term, these tools will be used for prognosis and for studying subtle temporal white matter changes which may be an indicator of pathology.

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5. REFERENCES

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